Section II (Remarks)

A. Summary of Amendment to the Claims

By the present Amendment, claim 18 has been amended; claims 1, 2, 5-9 and 23-29 have been cancelled; and new claims 30-36 have been added. Claims 3-4 and 21-22 were previously cancelled. No new matter within the meaning of 35 U.S.C. §132(a) has been introduced by the foregoing amendments.

The amendments made herein are fully consistent with and supported by the originally-filed disclosure of this application.

B. Propriety of Finality of Office Action mailed January 5, 2009

The Office Action mailed January 5, 2009 has been made final. MPEP §706.07(b) provides that an action may be made final on a first action after an RCE where

> "…all the claims in the application after the entry of the submission under 37 C.F.R. 1.114 (A) are drawn to the same invention claimed in the application prior to the entry of the submission under 37 C.F.R. 1.114 and (B) would have been properly finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to the filing of the RCE under 37 C.F.R. 1.114."

In a phone call with Examiner MacFarlane on March 4, 2009, the examiner maintained that the Office Action was intentionally been made final, based on the facts that 1) the new limitation added to claim 1 did not add any subject matter that significantly changed the claim, 2) new claim 29, as a dependent claim, did not add any new required subject matter to the claims, and 3) the rejection of the claims was based on the art of record, in the same combination as in the previous Final Office Action.

Applicants respectfully request that the examiner reconsider the finality of the Office Action mailed January 5, 2009. For a first action to properly be made final, MPEP §706.07(b) requires that the claims presented "would have been properly finally rejected on the grounds and art of record." Applicants respectfully submit that claims 1 and 29 would not have been properly rejected on the grounds of record, as these claims present new characteristics of the claimed invention, not previously considered

In the Submission provided with the RCE on October 10, 2008, two amendments were made to the claims. Claim 1 was amended to add the limitation "…wherein the non-activated TRP has a linear structure and, when activated…" and new claim 29 was added, reciting "The non-activated TRP of claim 1, wherein the TRP permeates a cell membrane without binding to a cell membrane receptor." It is respectfully submitted that claims 1 and 29 would not, in fact, "have been properly finally rejected on the grounds and art of record in the [Final Office Action mailed April 10, 2008]…"

In the Final Office Action mailed April 10, 2009, the examiner rejected the claims under 35 U.S.C. § 103(a) over the combination of Published U.S. Patent Application No. 2004/0197867, U.S. Patent No. 5,013,649 and Leighton, M., et al., J. Biol. Chem., (2003) p. 18478-18484, vol. 278, n. 20. With respect to claim 1, the examiner's arguments were based on the allegation that "the '649 patent and Leighton reference had already disclosed that it was known in the art that the 'furin activated domain' (FAD), comprising an amino acid sequence of the instantly-elected SEQ ID NO: 14, fused with the 'tissue regeneration domain' (TRD), comprising an amino acid sequence of the instantly-elected SEQ ID NO: 1, is the equivalent of the hBMP proprotein" and that "[t]he '867 publication discloses a fusion protein comprising PTD…fused to BMP2." (Office Action mailed April 10, 2008, p. 3-4.) The examiner further notes that "[i]f indeed these functional limitations structurally alter the claimed fusion protein, then it is upon the Applicant to demonstrate the structural difference." (Office Action mailed April 10, 2008, p. 4-5.)

By the Response filed with the RCE October 10, 2008, Applicants added the limitation to claim 1 reciting the linear structure of the resulting TRP. Additionally, Applicant provided an extensive line of argumentation demonstrating that by addition of such a limitation the claims recite polypeptides with structural as well as functional characteristics. The recited linear characteristic is essential to the claimed subject matter, as it places the polypeptide in a biologically inactive state.[1] The combination of references does not provide a polypeptide with the structure as claimed in the present application.

[1] The examiner has noted that allegations of biological inactivity might lead to a determination of lack of utility under 35 U.S.C. §101. (Office Action mailed January 5, 2009, p. 5.) However, the claimed polypeptide, even in an inactivated state, has utility in that it can be administered in that inactivated state, and subsequently activated after administration to stimulate the growth or formation of tissues or induce tissue regeneration. No issue under 35 U.S.C. §101 is presented by discussion of an inactivated state of the polypeptide.

In the Final Office Action mailed January 5, 2009, the examiner alleges that the cited combination of references applies to the amended claim "regardless of linear or 3-dimensional structure." (Office Action mailed April 10, 2008, p. 7.) Applicants respectfully disagree. The characteristic of structure is an essential characteristic of the claimed polypeptide. Further search or consideration should have been performed by the examiner in order to fully consider this claimed characteristic. Additionally, further lines of argumentation were provided by the examiner regarding the structural characteristic, such that the Final Office Action mailed January 5, 2009, though based on the same art, the same combination of references, contains new grounds of rejection.

New claim 29 is not included on page 3 of the Office Action mailed January 5, 2009 as a claim rejected under 35 U.S.C. §103. However, the claim appears to be addressed in passing on pages 8-9 of the Office Action. Specifically, the examiner alleges that "[t]he '867 publication teaches a cell permeable fusion protein…" and that the addition of claim 29 does not structurally limit the claimed polypeptide further. Further search or consideration should have been performed by the examiner in order to fully consider this claimed characteristic.

Withdrawal of the finality of the Office Action mailed January 5, 2009 is respectfully requested.

C. Rejection of Claims 1-9 and 18-28 Under 35 U.S.C. §103

In the Final Office Action mailed January 5, 2009, the examiner has maintained the rejection of claims 1-9 and 18-22 under 35 U.S.C. § 103(a) as unpatentable over Published U.S. Patent Application No. 2004/0197867 (hereinafter "the '867 publication"), further in view of U.S. Patent No. 5,013,649 (hereinafter "the '649 patent") and Leighton, M., et al., J. Biol. Chem., (2003) p. 18478-18484, vol. 278, n. 20 (hereinafter "Leighton et al."). By the present Response, claims 1, 2, 5-9 and 23-29 have been canceled and claims 30-35, dependent from claims 18, have been added. Applicants respectfully traverse the rejection and will address the rejection as it applies to all pending claims, 18-20 and 30-36.

Of the pending claims 18-20 and 30-35 claim 18 is an independent claim from which claims 19, 20, and 30-35 depend. The examiner's attention is respectfully drawn to amended claim 18, which recites:

> A composition for stimulating the formation or regeneration of tissue, containing the non-activated tissue-regeneration polypeptide (TRP) as an active ingredient wherein the non-activated TRP contains:
>
> (a) a protein transduction domain (PTD);
>
> (b) a furin activation domain (FAD) which has at least one proprotein convertase cleavage site and is cleaved by the proprotein convertase in cells; and
>
> (c) a non-activated tissue regeneration domain (TRD) which is activated by the proprotein convertase cleavage of the FAD,
>
> wherein the non-activated TRP has a linear structure and, when activated, stimulates the growth or formation of tissues or induces the regeneration of tissues.

New independent claim 36 recites:

> A method of stimulating the growth, formation or regeneration of tissue, comprising administration to a tissue growth, formation or regeneration locus of a non-activated tissue-regeneration polypeptide (TRP), wherein the non-activated TRP contains:
>
> (a) a protein transduction domain (PTD);
>
> (b) a furin activation domain (FAD) which has at least one proprotein convertase cleavage site and Is cleaved by the proprotein convertase in cells; and
>
> (c) a non-activated tissue regeneration domain (TRD) which is activated by the proprotein convertase cleavage of the FAD,
>
> and wherein the non-activated TRP has a linear structure and, when activated, stimulates the growth or formation of tissues or induces the regeneration of tissues.

In the Final Office Action mailed January 5, 2009, the examiner "maintains that the instant claims are drawn to a polypeptide and not a method of making nor a method of stimulating the growth or formulation of tissues…" (p. 7.) However claim 18 and the claims depending therefrom recite a composition for stimulating the formation or regeneration of tissue. Independent claim 36 recites a method for stimulating the growth, formation or regeneration of tissue. The pending claims contain, as a recited element, the activity and function of stimulation. However, as is also clear from the claims, that stimulation does not occur until the polypeptide, as an element of the composition of claim 18, is activated. The polypeptide is initially in an inactive state and when activated stimulates the growth, formation or regeneration of tissues.

In the Final Office Action at page 2, the examiner has stated that applicants' previous arguments were not persuasive. In response, applicants provide the following.

Claims 18-20 and 30-35 recite a composition containing a polypeptide, where the polypeptide is as previously cited in independent claim 1 and the composition recites the characteristics of stimulating the growth, formation or regeneration of tissues. Claim 36 recites a method of stimulating the growth, formation or regeneration of tissue.

The polypeptide contained within the claimed composition and method is distinguishable from the cited prior art in that the polypeptide affirmatively has a linear structure. The linear structure is recited in the pending claims. Generation of the polypeptides recited in the claims with the linear conformation provided a needed benefit over the prior art. As repeatedly stated in the application, prior art BMPs were known in a biochemically active state with the 3D structures shown in Figs. 1 and 2 and therefore difficult to separate, purify, store, handle and administer, due to the activity and conformation. (Specification, p. 3-4.)

The examiner states that "[t]he prior art teaches the generic form of the claimed polypeptide and this encompasses the polypeptide regardless of linear or 3-dimentional structure." Applicants respectfully disagree.

By the method of the '649 patent a protein is obtained that has a 3-dimensional structure illustrated by Fig. 2 of the present invention. BMP must have such structure in order to be secreted from a cell or to bind a receptor of cell surface. Accordingly, the prior art does not provide a generic form of the claimed polypeptide, but demonstrates a 3-dimensional structure only. The present invention provides an improvement over such structure in providing an inactivated, linear structure only.

The development by the present inventors of a linear structured polypeptide is not simply "discovery of a new property," as alleged by the examiner but is a wholly new polypeptide with a linear structure, in an inactivated state. The biologically inactive polypeptide, recited as an element in the composition and method claims, is produced from a prokaryotic organism (*E. coli*, using 8M Urea) and is denatured/unfolded into a linear structure, in order to maximize surface energy. This structure is shown in the application at Example 7 and in Figs. 21-23, 28, and 29. Since polypeptides of the present invention are denatured by 8M urea as described in the detailed description and the examples, they have no original 3-dimensional structure and therefore no biological activity and do not bind the BMP receptor of cell membrane. As is seen in Figs. 21-23, 28 and 29, polypeptides according to the present invention are mostly transduced into the

cells within one hour. Such characteristics are caused by high surface energy of non-structural denatured protein and PTD.

Accordingly, the polypeptide recited as an element in the claims has completely different physical and chemical characteristics from the protein of the '649 patent, as demonstrated by the above different characteristics and long felt need in the art.

The examiner further alleges that "Applicants arguments that the polypeptide of the claims is distinguished over that of the prior art is based upon the differences in the method of making and not to the structure of the sequences themselves." (Final Office Action mailed January 5, 2009, p. 7.) Applicants disagree with this characterization of their response.

Applicants have repeatedly stated, most recently in the Response mailed October 10, 2008, that a critical difference between the cited combination of prior art and the polypeptide of the claimed invention is that the prior art provides a polypeptide with a 3-dimensional structure and the claimed polypeptide has a linear structure. Indeed, Applicants do distinguish the claimed polypeptide over the prior art with a structure-based argument. Both of independent claims 18 and 36 recite "…wherein the non-activated TRP has a linear structure…" (Emphasis added.)

By elimination of a known problem in the art, the inability to administer polypeptides for growth, formation or regeneration of tissue, the inventors have provided a new and inventive linear polypeptide capable of *in vivo* activation in order to stimulate the growth, formation or regeneration of tissue. The present application therefore recites a novel composition and method for stimulating growth, formation or regeneration of tissue.

As the '867 publication in view of the '649 patent and Leighton et al. does not provide any logical basis for the composition or method recited in claims 18-20 and 30-36, the '867 publication in view of the '649 patent and Leighton et al. does not render the claimed invention obvious. Accordingly, withdrawal of the rejection of pending claims 18-20 under 35 U.S.C. § 103 (a) as being obvious over the '867 publication in view of the '649 patent and Leighton et al. is respectfully requested.

D. Fee Payable for Added Claims

By the present Amendment, 1 new independent claim and 7 new total claims have been introduced. The claims in the application now total 18 claims, 3 of which are independent. As the total number of claims does not exceed 20 total and 3 independent, no additional claims fees are believed due.

CONCLUSION

Based on the foregoing, all of Applicants' pending claims 18-20 and 30-36 are patentably distinguished over the art, and in form and condition for allowance. The examiner is requested to favorably consider the foregoing and to responsively issue a Notice of Allowance.

No fees are believed to be due for the filing of this paper. However, should any fees be required or an overpayment of fees made, please debit or credit our Deposit Account No. 08-3284, as necessary.

If any issues require further resolution, the examiner is requested to contact the undersigned attorneys at (919) 419-9350 to discuss same.

Respectfully submitted,

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